REMARKS

This Amendment and Remarks are filed in response to the Office Action dated October 4, 2006, wherein all claims are rejected.

Rejections Under 35 USC 112, First Paragraph

Claims 4-9, 12-17, 19 and 21-28 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Examiner argues that support is not found in the specification for the invention as now claimed. The page and lines should be pointed out where the specification discloses a method of the scope of claim 22 when using derivatized polyethylene glycol cross-linked with collagen as a sealant.

Applicants disagree. The term "derivatized PEG" is disclosed in the specification in several places. The claim 22 has now been amended to read "a derivatized polyethylene glycol (PEG) with tetrahydrosuccinimidyl or with tetra-thiol or PEG cross-linked with alkylated collagen". The support for this amendment is found, for example, on page 13, lines 3-6, 15 and 16; page 57, lines 14 and 15 and page 59, lines 3-6, 16 and 17. The method for treatment of an cartilage lesion is described in section IV, page 67. The method for formation of the superficial cartilage layer is described in section III, page 50.

In this regard, Applicants amended claims 19 and added a new claim 29, both dependent on claim 22 and both directed to the PEG cross-linked with methylated collagen sealant, supported on page 13, lines 3 and 4, page 59, lines 23.

Applicants believe that with this amendment, the rejection of claim 22 and dependent claims 19 and 29 are overcome and the claim is in a suitable form for allowance.

Examiner further argues that a method containing a combination of steps as required by claim 22 is not readily apparent in the

specification. The page and lines should be pointed out where each of the steps (a) - (f) of claim 23 are disclosed in combination as claimed.

Applicants disagree. Applicants amended claim 23 to be an independent claim comprising the steps (a)-(f), supported in the specification on the pages and lines as indicated. The method generally is disclosed in the specification, pages 4-7. Specifically, steps are described on page 17, lines 19-37, and page 18, lines 1-5. Detailed support is to be found on page 22, for preparation of neo-cartilage; page 23, isolation of chondrocytes; page 24, expansion of chondrocytes and suspension and seeding chondrocytes in a support matrix; page 27, preparation of the support matrix; page 33, processing neo-cartilage as in step (d); page 38, conditions for propagation of chondrocytes; page 59, implanting the neo-cartilage construct; page 17, lines 35-37, page 19, lines 3-5, among others.

Applicants submit that the claim 23, as amended is fully supported in the specification, as indicated above and that the rejection under 35 USC 112, first paragraph is overcome.

Concerning the support for claim 4 that Examiner argues is not readily apparent for the conditions of claim 4, as amended, Applicants disclosed features claimed in claim 4 on page 11, lines 23-36, where a gel, sol-gel, sponge, scaffold and hydrogel are disclosed as well as the compounds used for their preparation; page 29, lines 34-37 where honeycomb and lattice are described.

Claim 4 is fully supported in the specification as shown.

Concerning the support for claim 19 that Examiner argues is not readily apparent for the conditions of Claim 19 as amended, support can be found on page 69, lines 21-30, with verbatim language of claim 19, as amended, appearing in lines 26-30.

The claim 19 is supported in the specification. The rejection should be withdrawn.

Support for the conditions of new claims 26-28 is found on page 69, lines 24-29 for claim 28, and lines 26 and 27 for claim 26. Claim 27 is canceled as it would be duplicative of claim 19.

Applicants respectfully submit that all claims rejected under 35 USC 112, first paragraphs, as amended, are fully supported in the specification, as indicated above, and that the rejection under 35 USC 112, first paragraph is overcome and should be withdrawn. It is so respectfully requested.

Rejections Under 35 USC 112, Second Paragraph

Claims 4-9, 12-17, 19 and 21-28 are rejected under 35 U.S.C. 112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Examiner argues that Claim 6 is improperly dependent on claim 23 by including cells that differentiate into chondrocytes since claim 23 is limited to only chondrocytes. Furthermore the chondrocytes required in claim 6 appear to be already required in claim 23.

Applicants disagree, however they amended claim 6 to be directed to cultured and differentiated autologous or heterologous chondrocytes and claim 23 to be directed to autologous or heterologous chondrocytes or to cells that could be differentiated into chondrocytes.

Examiner argues that in claim 22 and where recited in other claims, the terms "superficial cartilage layer", "neo-cartilage construct" and "neo-cartilage implant" are uncertain as to meaning and scope. According to the Examiner, being "neo and superficial" is relative and subjective. Additionally there is not clear antecedent basis for "said neo-cartilage implant" in line 4 of claim 22.

Applicants disagree. Claim 22 is amended and the term "said neo-cartilage implant" is changed to "said neo-cartilage construct".

Concerning the term "neo-cartilage", such term describes an immature hyaline cartilage (neo-cartilage) construct and is defined on page 12, lines 3-5. The term "neo-cartilage" is further defined on page 22, line 1-9, as "an immature hyaline cartilage wherein the ratio of extracellular matrix to chondrocytes is lower than in

mature hyaline cartilage". The ratio of extracellular matrix to chondrocytes in mature hyaline cartilage is 95:5% of the matrix to the chondrocytes. This ratio is disclosed on page 22, lines 5 and 6. Inactive mature non-dividing chondrocytes are disclosed on page 20, lines 19-21 and on page 22, lines 9-21. Additionally, the concept of the neo-cartilage is disclosed throughout the specification, particularly on page 17, lines 1-8 and on page 22, lines 1-36 and in other places.

Concerning the term "superficial cartilage layer", such term is defined on page 14, lines 14-18 and is further disclosed, for example, on page 4, lines 31-36 wherein said superficial cartilage layer is described as sealing the cartilage lesion in situ, on page 18, lines 6-10 and in greater detail on page 50 and subsequent pages describing a method for formation of the superficial cartilage layer.

It is believed that both the "neo-cartilage" and "superficial cartilage layer" terms are sufficiently described in the specification that any person skilled in the art would understand what is meant by these terms in reference to the specification and in definitions.

Examiner further argues that on line 6 of claim 22,the term "derivatized polyethylene glycol" is uncertain as to the modification of polyethylene glycol that is a derivative. According to the Examiner, modified forms of polyethylene glycols that are derivatives are not found in the specification.

Applicants disagree. The term "derivatized polyethylene glycol" is found in several places in the specification. The claim 22 has now been amended to introduce some of these derivatives and it now reads "a derivatized polyethylene glycol (PEG) with tetrahydrosuccinimidyl or with tetra-thiol or PEG cross-linked with alkylated collagen". The support for this amendment is found, for example, on page 13, lines 3-6, 15 and 16; page 57, lines 14 and 15 and page 59, lines 3-6, 16 and 17.

Claim 22 is unclear as to where in the method the superficial cartilage layer is formed since the steps carried out do not

require a final step that produces the layer.

Applicants disagree. However, to expedite the prosecution, Claim 22 is now amended to include language specifying the step of depositing said top layer and resulting in formation of the superficial cartilage layer covering and protecting the implant.

With the amendment of Claim 22 the rejection is overcome.

Examiner further questions step b) of claim 23, and requires clarification of the difference between a "sol" and "sol-gel". Examiner argues that the difference is uncertain and if the sol-gel is a gelled sol, this should be made clear.

Applicants disagree. the terms "sol" and "gel" are two different
physical stages of the material. The sol is a colloidal dispersion in a liquid. The gel is a jellylike substance formed by a coagulation of a colloidal solution into a solid state. There are some materials that can be in sol (liquid) state at cold or warm temperature and gel at cold temperature. These are called sol-gel materials.

In line 7 of step d) of claim 23, the meaning and scope of "medium flow rate" is, according to the Examiner, uncertain. Being medium is relative and subjective. Additionally, in this line, it is uncertain how temperature" and "time" are conditions promoting activation. Time and temperature exist in any environment.

Applicants disagree. Applicants amended claim 23, step d) to clarify points Examiner is making, namely the "flow" is defined as "a flow of a culture medium", not a medium, low or high flow, as Examiner seemed to read the prior language. Temperature is defined as a temperature under which the activation and propagation of the chondrocytes is performed and time as a length of time.

Applicants submit that the questioned terms are well known to one of skill in this art. However, Claim 23 is now amended utilizing the qualifying language for these terms which is understood by one of skilled in the art.

Examiner further argues that Claim 23 is unclear with regard to where in claim 22 the steps of claim 23 are carried out. The

steps of claim 23 constitute a complete method without depending on claim 22, and the claim should be in independent form. Furthermore, when depending on claim 22, the sealant cannot be polyethylene glycol cross-linked with methylated collagen in claim 23 since the sealant in claim 22 is limited to a derivatized polyethylene glycol cross-linked with collagen.

Applicants disagree. Claim 23 is now amended to be independent taking in consideration Examiner's rejections.

With all amendments made in response of the rejections under 35 USC 112, second paragraph, it is believed that all rejections have been overcome and that the claims are now in conditions for allowance.

Examiner's response to the prior Applicants argument has been reviewed and considered and is already partly responded to above. It is Applicants understanding that the specification defines the invention and that the claims are read in view of the specification and that if any term in the claims needs further clarification, and such clarification is detailed in the specification, the meaning of the term and the claims are interpreted in view of the specification. Applicants disagree that in the scope of this particular invention the term "neo-cartilage" is uncertain as the whole specification and invention concerns the neo-cartilage, that is newly prepared neo-cartilage construct using activated and propagated chondrocytes into metabolically active chondrocytes resembling the immature chondrocytes. In "non neo-cartilage", that is in a mature cartilage, chondrocytes are mature and metabolically inactive. Similarly "superficial cartilage layer" is clearly described as the layer covering the implanted neo-cartilage construct where such layer is formed following deposition of the top sealant.

Applicants, however, would consider further amending the questioned terms in the claims if Examiner would find these claims otherwise allowable.

Rejections Under 35 USC 103

Claims 4-6, 12-17, 19, 21-23 and 26-28 are rejected under 35

U.S.C. 103(a) as being unpatentable over Smith et al (6,528,052 1) in view of Wise et al (American Surgeon) and Rhee et al(5,475,052), and if necessary in further view of Rhee et al (5,565,519) (Wise et al and Rhee et al references newly applied).

Examiner argues that the claims are drawn to a method for treatment of an articulate cartilage lesion and for formation of a superficial cartilage layer by surgically implanting a neo-cartilage construct into the lesion, and covering the construct with a layer of a top adhesive sealant that is derivatized polyethylene glycol (PEG) cross-linked with collagen. In claim 23 the method is carried out by isolating chondrocytes from cartilage, expanding and suspending the chondrocytes, seeding the chondrocyte suspension into a support matrix, preparing a neo-cartilage construct by subjecting the seeded support to conditions that promote activation and propagation of the chondrocytes, implanting the construct in a cartilage lesion, and depositing over the construct a top adhesive sealant that is PEG cross-linked with methylated collagen.

Examiner argues that Smith et al disclose formation of cartilage tissue *in vitro* from chondrocytes and implanting the cartilage (col 9, lines 22-33). The cartilage is formed by isolating cartilage cells, and culturing the cells while in a scaffold or support (col 9, line 30). The resultant cartilage tissue is transferred to a defect (col 9, lines 35-40).

Examiner argues that Wise et al disclose using a collagen-polyethylene glycol sealant to seal leaks after liver transplantation.

Examiner further argues that Rhee et al ('052) disclose using a collagen-polyethylene glycol matrix (cols 15-17 and col 20, line 60 to col 23, line 67) for implant applications and that Rhee et al ('519) disclose using a collagen-polyethylene glycol conjugate for ophthalmic applications (cols 9-20).

Examiner concludes that it would have been obvious to seal a defect after implanting cartilage tissue in a defect as disclosed by Smith et al using a collagen-polyethylene glycol sealant as

suggested by Wise et al using this sealant and Rhee et al using a collagen-polyethylene glycol matrix for implant applications.

Further, Examiner maintains that it would have been obvious that sealing the defect after implanting will be advantageous to prevent contamination and infection at the site of the defect and that the cartilage produced by Smith et al before implanting is inherently a construct.

Examiner further argues that, if needed, Rhee et al ('519) would have further suggested using a collagen-polyethylene glycol sealant from disclosing using a collagen-polyethylene glycol conjugate for ophthalmic applications. A hydrostatic pressure as in claim 12 is disclosed by Smith et al. Methylated collagen as in claim 23 is taught by Rhee et al ('052) (col 16, line 29). The parent application does not antedate Wise et al since the presently claimed invention is not disclosed in the parent application.

Applicants disagree. The combination of the above references, as Examiner is suggesting is not obvious. First, Smith reference does not prepare neo-cartilage construct as disclosed in the current invention and does not suggest use of any sealant.

Smith, et al ('052) teaches methods for *in vivo*, *ex vivo* and *in vitro* repair and regeneration of cartilage and collagen and also for bone remodeling. Smith reference concerns a discovery that intermittently and repeatedly applied hydrostatic pressure during interval loading periods influences articular chondrocyte gene expression, elicits load-dependent collagen type II expression, decreases a matrix metalloproteinase expression, results in regeneration of diseased or damaged cartilage and collagen and permits the *de novo* formation of mesenchymal or mesenchymally-derived cells within a matrix. Col. 6, lines 61-67 and col.7, lines 1 and 2. The whole Smith reference relates to this discovery.

Examiner points out Col. 9, lines 22 and 23 of Smith reference as disclosing formation of cartilage tissue from chondrocytes and implanting the cartilage, Col 9, line 30 and lines 35-40 as disclosing isolating and culturing cells while in a scaffold/support and transferring the resultant tissue to a defect.

Applicants point out to the Examiner that the Smith reference deals with treatment of the diseased or injured cartilage or with production of the new cartilage by providing means for treatment, herein called the algorithm, of the cells or tissue in order to enable this tissue to recover, repair itself or form the new tissue. At best the Smith reference may be related to the current invention as the reference showing that certain conditions permit the cartilage tissue to recover *in vivo* by applying the algorithm of Smith, or *ex vivo*, by treating the osteochondro cartilage graph, or *in vitro*, by treating cartilage cells cultured in suspension in the scaffold support.

The current invention utilizes similar steps to those disclosed in Smith for preparation of the neo-cartilage construct. However, the neo-cartilage construct is in fact the implantable structure that is implanted into a cartilage lesion in conjunction with the tissue adhesive that have been demonstrated to be involved in the healing process and in formation of the new covering layer over the treated lesion. The invention thus extends the utility of Smith invention to result in production of the contiguous layer of the cells over the treated cartilage lesion that is interconnected with the surrounding native synovial tissue, namely in the formation of the superficial cartilage layer that is integrated into the native tissue.

Examiner argues that the use of the sealant would be obvious to close the wound and protect it from the outside environment. However, the use of the current adhesive sealant, and it should be noted, the use of the specific polyethylene glycol cross-linked with alkylated, preferably methylated ,collagen sealant, has been found, surprisingly, to result in the newly formed structural tissue layer, herein called superficial cartilage layer, that is, with time, integrated into the synovial membrane covering the uninjured cartilage.

Applicants specification, Figures 10B and 12A and 12B clearly show the formation of the superficial cartilage layer compared to the untreated lesion (Figure 10A) and formation of fibrocartilage

in defects that were not covered with the adhesive sealant, seen in Figures 11A and 11B.

Should the Examiner's argument be valid, then the untreated defect, as seen in Figures 11A and 11B, could be contaminated and/or infected during and after surgery. Quite clearly, the arthroscopic surgeries are performed in sterile conditions and typically do not result in contaminations or infections and expectation that the site would be contaminated during surgery is not a reason to use the sealant. During arthroscopic procedures using implant, such implant is typically attached and secured with microsutures.

The current results show that when, instead of the microsutures, the adhesive sealant is used and applied over the implant, this particular sealant not only seals the implant within the lesion cavity but it does integrates with the surrounding tissue and within certain period of time, typically from one week to several months, (Spec., page 18, lines 16-18) leads to formation of what is called here the superficial cartilage layer, that is integrated into the native synovial membrane of the surrounding tissue. Additionally, as described in figures 10B and 12A and 12B, the neo-cartilage implant covered with this sealant leads to restoration of the hyaline cartilage rather than to the formation of fibrocartilage, as seen in Figures 11A and 11B. The defect, treated according to the invention thus restores the cartilage to its pre-injury quality tissue but it also is overgrown with a newly formed membrane resulting from the application of the top sealant over the neo-cartilage implant.

Moreover, while it seems obvious to Examiner to do so, it is not currently the practice to cover the implant with any kind of glue when the various implants are used for repair of the cartilage. Additionally, as already pointed out, the invention does not utilize any kind of sealant but a specific tissue adhesive that must contain derivatized collagen cross-linked with polyethylene glycol and only this type of the tissue adhesive was shown to result in formation of the superficial cartilage layer.

Independent claim 23 is amended to read in step (f) "depositing the top biocompatible adhesive sealant over the neo-cartilage construct wherein said top sealant is the polyethylene glycol cross-linked with methylated collagen, wherein said deposition of said top sealant over said implanted neo-cartilage construct results in formation of the superficial cartilage layer that overgrows and protects said neo-cartilage construct implanted within said lesion".

Smith does not in any way suggest, imply or disclose use of any sealant or tissue adhesive, top or bottom, and it definitely does not give any notion that such use could lead to formation of the protective superficial cartilage layer overgrowing the treated cartilage. Thus to make this invention obvious, Smith alone or in combination with other cited references would have to suggests, disclose or indicate that such superficial layer is formed, and such suggestion is nowhere to be found and, in fact, without using this specific sealant, **such superficial cartilage layer is not formed**.

Applicants respectfully submit that none of the references or their combination provides any kind of suggestion or implies that such formation would happen.

Wise et al discloses sealant used for bile leaks in liver transplantation. The specific material, absorbable polyethylene glycol/collagen biopolymer sealant (CT3 Surgical Sealant, Wise, page 1, lines 2 and 3), disclosed by Wise is a true surgical sealant that acts as a sealant in an acute situation, and is used to stem the flow of bile after/during a liver transplantation. Examiner should note that the sealant Wise is using is not derivatized polyethylene glycol or polyethylene glycol cross-linked with derivatized (alkylated, particularly methylated) collagen. Additionally, Examiner should note, that the liver is the soft tissue compared to the hard cartilage tissue subjected constantly to pressure, rotation, shearing and other forces employed during knee or joint movements and rotation. There is no need for long term presence of the sealant following the transplantation and the

sealant is therefore quickly absorbable (Wise, line 2, page 1).

Applicants respectfully submit that the Wise' use of the **different sealant** for **different tissue** and **different medical application** does not make the current invention obvious. How could application of the different sealant to the bile leakage during liver transplantation suggest that the different sealant would be useful to hold the joint implant in place in a hard joint surface environment long enough, and also that it would interact with and integrate into the patient own tissue overgrowing the cartilage lesion. It is worth noting that the cartilage lesion is a place where currently used implantations require 50-100 microsutures to keep the implant in place. There is no assurance from the Wise reference that the kind of joint stresses, such as knee bending or continuous passive motion that the Wise sealant would be subjected to would be possible, since there are no such stresses in the bile reconstruction system.

Additionally, with regard to applicability of the Wise reference, there is a question of live and dead cells. No live-dead cell studies were made by Wise mainly because in an acute state, i.e. transplantation, no one is concerned with how many cells are killed initially during the sealant polymerization as long as stanching the flow of bile occurs, and the tissue can recover. But in a system such as the present invention, where applicants are implanting developing tissue (neo-cartilage), the number of cells killed is of the gravest importance. Hence, it is not obvious that Wise sealant is useful in this system.

Rhee et al ('052) teaches various collagen-synthetic polymer materials for use as the matrices. However, Examiner will note that these materials are suitable to be used for preparation of various collagen-synthetic polymer matrices and biocompatible implants but not for use as tissue sealants. Additionally, not even the use for preparation of implants for joint cartilage is disclosed in '052 reference. Since no use as the sealant is disclosed and since the use and materials are different and the purpose of their use is different, Applicants respectfully argue

that the reference alone or in combination with other references does not even point out to the current invention not to say making it obvious.

Should Examiner wish to argue that the '052 reference is related to the implant, that is to neo-cartilage construct, as for example the matrix, of the invention, Applicants respectfully point out that the current neo-cartilage construct comprises a collagen gel, sol-gel or hydrogel suspension of chondrocytes seeded into the matrix and the chondrocytes are activated with the algorith conditions. While it could maybe be possible to use some of the materials disclosed by Rhee ('052), as a matrix material it would require undue experimentation to do so in order to determine if the activated chondrocytes could be seeded into such matrix and, primarily, if they would survive in these environments. The subject is discussed in the current specification, page 26, lines 29-32. Also, neither the cartilage tissue or any use of the Rhee's materials for treatment or sealing of the cartilage tissue is disclosed in the reference.

Rhee et al ('519) teaches conjugates for ophthalmic application.

Not to repeat the arguments already submitted above, Applicants respectfully submit that the ophthalmic use does not in any way suggest the use of the sealant in hard tissue, such as the joint cartilage. Applicants direct Examiner's attention to the col. 19, lines 26 to lines 67 where the various uses of the various forms of chemically modified collagen covalently cross-linked with synthetic hydrophilic polymers, such as polyethylene glycol cross-linked with methylated collagen, are described as useful for ophthalmic use, devices and materials that are relatively transparent to visible light. Disclosed uses are, for example, vitreous humor replacement, corneal shields, artificial corneal implants and/or delivery of various drugs.

There is no teaching or suggestion in any of the cited references to combine them in a general or specific way to obtain Applicants present invention.

Applicants submit that the present invention is not obvious in view of these references, alone or in any kind of combination.

Reconsideration and withdrawal are respectfully requested.

Response to Arguments

Examiner's response to Applicants' prior argument has been considered but it is deemed inaccurate. Examiner submits that after implanting, a sealant would have been obvious to close the wound resulting from surgical implantation against the outside environment for the same reason that a bandage is placed on wound. There is no outside environment with which the wound would come in contact during and after arthroscopy. Besides, it is not for closing the wound that the sealant is applied over the implant. Examiner claims that formation of a superficial cartilage layer will be inherent as the defect heals. From the Figures 11A and 11B, it is quite clear that when the defect heals without the current intervention, such healing results in formation of fibrocartilage and no superficial cartilage layer is formed. Examiner claims that Smith et al is not applied alone, but in combination with Wise et al and Rhee et al ('052), and if needed Rhee et al ('519), and these references would have suggested a collagen-polyethylene glycol sealant. There is no suggestion of any need for sealant in Smith. There is no suggestion of using Rhee ('052) or ('519) as a sealant for cartilage tissue.

Additional arguments were made above.

Double Patenting

Claims 4-9, 12-17, 19 and 21-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 2-5, 7-9 and 21-29 of copending Application No. 10/625,822. Although the conflicting claims are not identical, they are not patentably distinct from each other because the present claims of treatment of articulate cartilage using a top sealant, or top and bottom sealants, would have been obvious from the claimed method of the copending application for repairing articular cartilage using top and bottom sealants.

This is a provisional obviousness-type double patenting

rejection because the conflicting claims have not in fact been patented.

Applicants disagree. However, to advance this prosecution, Applicants submit a fully executed Terminal Disclaimer. The present application and U.S. Ser. No.: 10/625,822 are both assigned to Histogenics Corporation.

Thus, the double patenting rejection is overcome and should be withdrawn.

Double Patenting Rejection

Claims 4-6, 12-17, 19, 21-23 and 26-28 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 21-42 of copending Application No. 10/625,245 in view of Wise et al and Rhee et al (5,475,052), and if necessary in further view of Rhee et al (5,565,519).

For the type of reasons set forth above in the 103 rejection, it would have been obvious to seal a defect after implanting the construct of the copending application claims using a sealant suggested by Wise et al and Rhee et al ('052), and if needed Rhee et al ('519).

This is a provisional obviousness-type double patenting rejection.

Applicants disagree. However, to advance the prosecution, Applicants submit herewith a fully execute Terminal Disclaimer. The present application and U.S. Ser. No.: 10/625,245 are both assigned to Histogenics Corporation.

Reconsideration and withdrawal of double patenting rejection is respectfully requested.

Double Patenting Rejection

Claims 4-6; 12-17, 19; 21-23 and 26-28 are rejected on the ground Of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-16 of U.S. Patent No. 6,949,252 B2 in view of Wise et al and Rhee et al (5,475,052), and if necessary In further view of Rhee et al (5,565,519).

For the type of reasons set forth above in the 103 rejection, it would have been obvious to seal a defect after implanting the construct of the patent claims using a sealant suggested by Wise et al and Rhee et al ('052), and if needed Rhee et al ('519). Formation of a superficial cartilage layer will be inherent when the defect containing the sealed implanted construct heals.

Applicants disagree. However, to advance this prosecution, an executed Terminal Disclaimer and fees are submitted concurrently herewith. This application and U.S. Patent 6,949,252 are both assigned to Histogenics Corporation.

Withdrawal of the double patenting rejection is respectfully requested.

Double Patenting Rejections

Claims 4-6, 12-17, 19, 21-23 and 26-28 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-20 of U.S. Patent No. 6,528,052 B1 in view of Wise et al and Rhee et al (5,475,052), and if necessary in further view of Rhee et al (5,565,519) For the type of reasons set forth above, it would have been obvious to seal a defect after implanting the in vitro formed cartilage of claim 16 of the patent using a sealant suggested by Wise et al and Rhee et al ('052), and if needed Rhee et al ('519). Formation of a superficial cartilage layer will be inherent when the defect containing the sealed implanted construct heals.

Applicants disagree. Appropriate arguments to overcome this rejection are already made above. Additionally, Applicants amended claims to further distinguish them from these references. There is no double patenting present. None of the references deals with the formation of the superficial cartilage layer and with neo-cartilage.

The double patenting rejection is improper as the patent 6,528,052 is not Applicants patent. Withdrawal of the rejection is respectfully requested.

Claims Free of Prior Art

Applicants note with appreciation the Examiner's finding that claims 7-9, 24 and 25 are free of the prior art.

SUMMARY

In summary, claims are amended, new claim 29-37 are added and arguments provided to overcome rejection under 35 USC 103 and 112, first and second paragraphs. Double Patenting Rejections are overcome with appropriate Terminal Disclaimers.

Should Examiner find that additional amendments are necessary, Examiner is encouraged to call the undersigned at 650-324-1677.

The Commissioner is authorized to charge or credit Deposit Account No. 16-1331 as needed for filing this response.

Respectfully submitted,

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